REMARKS

The Rejection Under 35 U.S.C. § 112, First Paragraph for Lack of Written Description Should be Withdrawn

The Examiner has maintained the rejection of claims 84, 85, 88-91, 94-108 and 110 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. The Examiner continues to assert that the claimed subject matter is not described in the specification in a way as to reasonably convey to one skilled in the art that the inventors were in possession of the claimed invention at the time of filing. In addition, the Examiner asserted that claims 84, 85, 88-91, 94-108 and 110 introduce new matter into the specification because the claim-recited substrates are not supported by the specification.

Applicants traverse this rejection for all the reasons set out in the previous responses. To support these arguments, a Declaration of John Anderson, Ph.D. Under 37 C.F.R. 1.132 (denoted herein as the "Anderson Declaration") was provided with the previous response dated March 16, 2010. In particular, the Anderson Declaration provides evidence demonstrating: (1) who would be one of ordinary skill in the art in relation to the present invention, (2) what the specification teaches from the viewpoint of one of ordinary skill in the art, (3) how one of ordinary skill in the art views the written description provided in Table 6, and (4) that the Applicants were in possession of the claimed subgenus at the time of filing.

The pending claims are directed to methods of assaying for modulators of β-secretase activity using a substrate that 1) comprises an amino acid sequence of at least six amino acids, 2) comprises a β-secretase processing site defined by the formula P_2P_1-$P_{1'}P_{2'}$, wherein: P_2 is N; P_1 is F; $P_{1'}$ is E and $P_{2'}$ is A, and 3) is cleaved between P_1-$P_{1'}$ by a human aspartyl protease. Thus, the claim-recited substrates are limited to peptides comprising a processing site of NFEA. The number of members of the subgenus encompassed by the claims is not overly broad, and as explained in the previous responses and the Anderson Declaration, it is clear to one of ordinary skill in the art that Applicants were in possession of the claim-recited substrates.

Examiner Must Provide Reasoning Why the Anderson Declaration is Not Persuasive

The Examine acknowledged submission of the Anderson Declaration in response to the written description rejection. However, he failed to provide any particular reasoning why the Anderson Declaration does not rebut the rejection. According to MPEP § 2163.04, when maintaining a rejection for lack of written description, "any affidavits relevant to the 35 U.S.C. 112, para. 1, written description requirement, must be thoroughly analyzed and discussed in the next Office action. See *In re Alton, 76 F.3d 1168, 1176, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996).*"

When rejecting the claims under 35 U.S.C § 112, first paragraph, the initial burden is on the examiner to establish a prima facie case for lack of adequate written description by providing a reason why a skilled person in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. In response, Applicants provided the Anderson Declaration as evidence that a person skilled in the art at the time of filing would recognize from reading the specification and reviewing Table 6 that the inventors were in possession of the claims methods that use substrates having a cleavage site having the amino acid sequence NF-EA. Furthermore, patentability should be determined on the totality of the record, by a preponderance of the evidence, with due consideration to persuasiveness of the argument. *Id.* at 1175 citing *In re Oetiker, 977 F. 2d 1143, 1445 (Fed. Circ. 1992).*

Anderson Declaration Provides Evidence that the Claims are Adequately Described in the Specification

The Examiner's brief discussion of the Anderson Declaration is mainly at page 7 of the Office Action when providing his description of the "level of skill in the art." In particular, the Examiner stated that the Anderson Declaration purports that a reader understands Table 6 to provide a concise description of each of the 2,940 peptide substrates defined by selecting $P_2P_1P_1{\cdot}P_{2'}$ from the choices in Table 6. The Examiner continues to refer to Table 6 as a "laundry list" despite the fact that Dr. Anderson stated that "Table 6 on page 30 of the application represents a summary of the specific amino acid residues that are preferred at the cleavage site proximal positions. It is clear to me and it would have been

clear to a person of average skill in the field from Table 6 and related text that the inventors contemplated peptide substrates wherein P_2 is N, L, K, S, G, T, D, A, Q or E; P_1 is Y, L, M, Nle, F or H; $P_{1'}$ is E, A, D, M, Q, S or G; and $P_{2'}$ is V, A, N, T, L, F and S, each independently of the other. The reader understands Table 6 to provide a concise description of each of the 10x6x7x7=2,940 peptide substrates defined by independently selecting P_2 P_1 $P_{1'}$ and $P_{2'}$ from the choices provided in the Table." (see ¶C5 of the Anderson Declaration). The Examiner asserted that Dr. Anderson's calculation is incorrect because a reader would calculate the possible amino acid combination based upon $P_4P_3P_2P_1$-$P_{1'}P_{2'}P_{3'}P_{4'}$ which would yield 9,878,400 possible sequences. (See Office Action at page 8).

However, the claim reads that the substrate comprises a peptide having an amino acid sequence of at least 6 amino acids, not at least 8 amino acids as inferred by the Examiner, and the claims particularly defined the 4 amino acids at the P_2P_1-$P_{1'}P_{2'}$ positions flanking the β-secretase cleavage site. Therefore, in regards to the pending claims, Table 6 defines 4 residues and provides 2,940 combinations within the genus of 4 amino acid peptides in the P_2-$P_{2'}$ positions flanking the β-secretase cleavage site. Dr. Anderson's characterization of Table 6 is not overly generous. Rather, his characterization is consistent with the claims as pending and is not at odds with Table 6. Contrary to the Examiner's conclusion, the disclosure of Table 6 constitutes a written description of peptides having the formula P_2P_1-$P_{1'}P_{2'}$, wherein: P_2 is N; P_1 is F; $P_{1'}$ is E, $P_{2'}$ is A.

Furthermore, Dr. Anderson provides facts regarding the peptide core structure including that (1) these four residues are the most important to cleavage activity, (2) the inventors used amino acid substitution studies to deduce a genus of residues having similar physical properties that may be used at the given position to favor a cleavable substrate and (3) Table 6 represents a summary of the specific amino acids residues that are preferred at the cleavage site proximal positions. Dr. Anderson further states that it is clear to him and would have been clear to a person of average skill in the field from Table 6 in combination with related text, that the inventors contemplated peptide substrates having the core peptide structure of NF-EA. Regardless of the number of the members within the genus disclosed by Table 6, the Examiner does not provide any reasoning as to why these facts provided by Dr.

Anderson do not rebut the written description rejection, but rather continues to refer to the summary of Table 6 as a "laundry list."

The Examiner quoted the Federal Circuit in *Vas-Cath v. Mahurkah 935 F2d 1555 (1991)* stating that "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met." (See Office Action, page 9) The Anderson Declaration provides evidence that a skilled artisan would have understood from reading Table 6 and the related text that the inventors were in possession of the claimed invention at the time of filing. Thus, the written description rejection should be withdrawn.

Possession of Substrates having the Processing Site NFEA

At page 11 of the Office Action, the Examiner disputed Dr. Anderson's statement that the previously cited references (Gruninger-Leitch *et al.*, Majer *et al.*, Saunder *et al.*, Tomasselli *et al.*, and Shi *et al.*) in combination with additional references (Oliveriria et al. and Andrau et al.) "demonstrate that the vast majority of the peptide substrates disclosed in Table 6 of the patent application will be cleaved by β-secretase." (see ¶ D11 of the Anderson Declaration). To support his position, the Examiner pointed to Table 3 of WO 02/094985 (referred to as PCT '985), acknowledged that PCT '985 describes an amino acid sequence comprising NF-EV, which shares three amino acids with the elected sequence. However, Table 3 of PCT '985 also provides data for SEQ ID NO: 260 (EVNFEAEF), which comprises the elected peptide and is cleaved 17x more efficiently than a peptide comprising the wild type cleavage site (EVNLDAEF) (see page 42 of PCT '985). The Examiner has overlooked this data in Table 3 of PCT '985. Therefore, the Examiner's reasoning to dispute Dr. Anderson's statements is flawed.

In addition, the Examiner remarked that "Applicant's assertion that 'WO 02/094985 also provides confirmation of sufficient disclosure of β-secretase substrates' appears to support the position that certain issues were still not resolved or did not overcome the unpredictability that results in undue experimentation." (See Office Action at page 11). The references to post-filing data in the Anderson Declaration and in previous responses are

not an admission that issues were not resolved. Table 6 provides peptides tested in PCT '985. Applicants are not required to test every substrate encompassed by the invention. *In re Angstradt 537F. 2d 498, 502-503 (1976).* The Anderson Declaration provides evidence that a skilled artisan would expect the majority of the peptides taught in Table 6 to be cleaved by β-secretase and the post-filing data confirms the teachings in the specification that peptides comprising the cleavage site NF-EA are cleaved by β-secretase.

The Examiner disputed that the specification or the teachings in the art provide a well-established correlation between structure and function of peptides comprising the cleavage site of NF-EA. The Examiner also stated that the specification is little more than an outline of goals that the Applicants hope the claimed invention achieves. The specification teaches the structure of the peptide substrates by provding Table 6, which according to Dr. Anderson, a skilled artisan would recognize as a substrate of the invention. Furthermore, Table 6 provides the location of the bond to be cleaved (between the F and E), and provides the enzyme that cleaves the peptide. The disclosure provides an actual amino acid sequence and states the function, which is proven to be fact in a post-filing publication (PCT '985). This is not a mere wish comparable to the facts in Amgen where the actual structure of the claimed molecule is not provided. (Examiner cited to *Amgen v. Chigai Pharma. 927 F. 2d 1200 (1991)* at p. 12 of Office Action). Furthermore, Table 6 is not a partial disclosure; rather as Dr. Anderson states at paragraph C5, Table 6 is a short hand way to disclose the amino acid sequence (actual structure) of the peptides of the invention.

The Negative Limitation in Claim 84

The Examiner stated that the claim limitation "wherein the peptide does not comprise the corresponding P_2P_1-$P_{1'}P_{2'}$ portion of amino acid sequence depicted in SEQ ID NO: 19....SEQ ID NO: 39" conflicts with the claimed amino acid sequence of NF-EA and this limitation would suggest to a skilled artisan not to select the peptides encompassed by the claims. This paragraph in claim 84 is a negative limitation that disclaims any of the known substrates set out in SEQ ID NOS: 19-39. According to MPEP 2173.05(i), a negative limitation in a claim is permissible and there is nothing inherently ambiguous or uncertain about negative limitations. One of skill in the art will understand that the sequences that were

dedicated to the public prior to filing (SEQ ID NOS: 19-39) were not intended to be encompassed by the claims.

Nevertheless, the Examiner is incorrect in asserting that the amino acid sequences of SEQ ID NO: 19 (AEVNLDAEFR) and SEQ ID NO: 34 (SSNFAVGA) directly conflict with the elected peptide. The claim recited peptide of NFEA is not comprised by the amino acids sequences of SEQ ID NO: 19 and SEQ ID NO: 34. Thus, the Examiner's objections relating to the negative limitation in claim 84 are moot.

New Matter

The Examiner maintained the rejection under 35 U.S.C. § 112, first paragraph for new matter because the peptide of NF-EA is not adequately described in the specification. As described in detail above, the claims are supported in the specification by the disclosure in Table 6. Thus, the addition of claims 84 and its dependents is not new matter and the rejection should be withdrawn.

CONCLUSION

In view of the evidence provided in the Anderson Declaration and the above remarks, the claims satisfy the written description requirement and the rejection under 35 U.S.C. § 112, first paragraph should be withdrawn. Applicants believe pending claims 84, 85, 88-91, 94-108 and 100 are in condition for allowance. Applicants respectfully request reconsideration and withdrawal of all rejections and allowance of the claims currently under examination.

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Respectfully submitted,

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